UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,879	07/21/2006	Masako Nakazawa	293592US0PCT	8110

22850 7590 10/06/2009

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
PAGONAKIS, ANNA	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,879	NAKAZAWA ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/28/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-25* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8 and 11-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 7/22/2009 have been received and entered into the present application.

Applicant's arguments, filed 7/2/2009 have been fully considered. Newly added claims 9-10 are withdrawn from consideration as being directed to a non-elected subject matter. Please see 37 C.F.R. 1.142(b) and MPEP 821.03. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claims 1-2, 4, and 6-25 are currently under examination and the subject of this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 8, 11, 13, 15-17, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant claims "percent by weight" in claims 6, 11, 13, 15-17, 20 and 22. Though Applicant claims "by weight" it is unclear to what the "by weight" is drawn to. In other words, by weight of what?

In any case, it is not clear what applicant intends to claim, and as such fails to distinctly point out the subject matter to which the applicant regards as the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 6-8, 11-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

Present claims are directed to an injectable aqueous solution preparation having a pH from 2 to 5, the preparation comprising water and 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin and acetic acid and sodium acetate that render 7-ethyl-10-piperidinopiperidinocarbonyloxycamptothecin soluble by itself at a pH of 2 to 5. The specification and claims as originally filed fail to provide adequate written description for the newly amended limitation of that render "7-ethyl-10 piperidinopiperidinocarbonyloxycamptothecin soluble by itself at a pH of 2 to 5."
Applicant has not provided Applicant any direction as to where the newly added claim limitations can be found in the instant disclosure. Upon review of the disclosure, no such limitations was found. While it is recognized that adequate written description of a limitation is not required to be stated in *haec verba* in the specification or claims as originally filed, adequate written support for all claim limitations must arise from either an explicit or implicit suggestion by the disclosure to show that such a concept as now claimed was actually in possession of the Applicant at the time of the invention.

MPEP 2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement, does the description clearly allow persons of ordinary skill in the art to recognize that he or she invention what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10

USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-1564, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter," *Ralston Purina Co. v. Far-Mar-Co., Inc.* 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))… Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6-7, 13-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (U.S. 2003/0211180 in view of Ahmad et al (U.S. 2006/0030578) and Messerer et al. (Clin Cancer Res, 2004, 10(19): 6638-49, abstract).

Cheng et al. teach of an internal standard solution consisting of irinotecan with acetonitrile and glacial acetic acid (paragraph [0266]). Further it is taught that irinotecan exhibits anti-tumor activity in cancer patients (paragraph [0101]).

Ahmad et al. teach that sodium acetate and acetic acid are both acidic aqueous buffers for the liposomal irinotecan composition.

Messerer et al. teaches the intravenous administration of liposomal irinotecan (abstract).

It would have been prima facie obvious to one of ordinary skill in the art to substitute the glacial acetic acid of Ahmad et al for the acetic acid in the composition of Cheng et al because both sodium acetate and acetic acid are functional equivalents (i.e. acidic buffering agents), one of ordinary skill in the art would have been motivated to substitute the glacial acetic acid per Cheng et al. with sodium acetate and expect the composition to have similar activity. Further, one would have been motivated to administer the composition of Ahmad et al. because Messerer et al. teaches that liposomal irinotecan compositions are known to be administered intravenously.

The determination of the optimum pH of the claimed liquid dosage form would also have been a matter well within the purview of the skilled artisan. Such a determination would also have been made in accordance with a variety of factors, such as modifying the pharmaceutical carriers used to formulate the dosage form to optimize palatability of the dosage form and to maximize tolerability of the composition.

In addition, the skilled artisan would also have been motivated to optimize the pH of the solution in order to maintain the active pharmaceutical ingredients in their desired salt form without any degradation of the active ingredients that may occur due to a change in pH.

Further, it would have been obvious to vary the amount of different components and ratio between those different components as well as schedule of administration because it is well within the skill of the artisan at the time of the invention and would have not required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included to diet and medical condition of the patient, severity of the disease, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed and whether the compound is administered as part of a drug combination, as in the present case.

Claims 1, 4, 6-7, 13-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (U.S. 2003/0211180 in view of Ahmad et al (U.S. 2006/0030578) and Messerer et al. (Clin Cancer Res, 2004, 10(19): 6638-49, abstract) as applied to claims 1, 4, 8, 11-12 and 19-21 above, and further in view of Chen et al (U.S. 6,383,471).

The combination of Cheng et al (U.S. 2003/0211180 in view of Ahmad et al (U.S. 2006/0030578) as evidenced by MeSH Supplementary Concept Data (2008) is set forth supra. The combination differs by not comprising component (C) of claim 2.

Chen et al teach of a composition suitable for use in oral dosage (abstract). A therapeutic agent taught is irinotecan (claim 12). The solubilizer of the instant invention includes propylene glycol and cyclodextrin (column 3). Suitable bases include acetic acid and ascorbic acid (column 11).

It would have been *prima facie* obvious to the skilled artisan at the time the invention was made to additionally add the instantly claimed solubilizers and bases to form the instant composition because it is known in the prior art that this composition is suitable for use in oral dosage.

Further, it would have been obvious to vary the amount of different components and ratio between those different components as well as schedule of administration because it is well within the skill of the artisan at the time of the invention and would have not required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included to diet and medical condition of the patient, severity of the disease, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed and whether the compound is administered as part of a drug combination, as in the present case.

Claims 1, 4, 6-7, 13-18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (U.S. 2003/0211180) in view of Ahmad et al (U.S. 2006/0030578) and Messerer et al. (Clin Cancer Res, 2004, 10(19): 6638-49, abstract) as combined supra for claims 17 and 18 further in view of Remington's Pharmaceutical Sciences (pages 420-425, 1980).

The combination differs by not teaching salt forms. The use of pharmaceutically acceptable salts of the elected compound would have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of a drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been *prima facie* obvious to the skilled artisan motivated by any one or more of these factors to formulate the active agent into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to

reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the agent itself.

Response to Applicant's Remarks

Applicant alleges that the composition of Ahmad et al. is not soluble by itself but only in a lipid complex. Ahmad et al. does teach an aqueous solution of irinotecan (paragraph [0013]). Though, as noted by Applicant this occurs after re-hydration of the lipid phase, it remains that the irinotecan absent the lipid phase is soluble. Further, it is taught that the aqueous solution can have the desired pH from addition or the appropriate buffers (paragraph [0027]). *Applicant alleges that Ahmad et al. teaches chloroform and ethanol as well as other compounds which are not suitable for injection.* This assertion by Counsel is an unsupported allegation and fails to take place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with guidance provided at MPEP 2145, which states "The arguments of counsel cannot take the place of evidence in the record."

The rejection is maintained for the reasons above and those already made of record.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614